PI(s) of MSM U01: Scott A. Berceli, Marc Garbey
Institution(s): Malcom Randall VAMC, Gainesville, FL / Houston Methodist Hospital, Houston, TX
MSM U01 Grant Number: HL119178-01
Title of Grant: Constitutive and Agent-Based Multiscale Models to Improve Vein Graft Survival

Abstract Authors
Stefano Casarin, Marc Garbey, Scott A. Berceli

Abstract Text
The long term outcome of Vein Graft Bypass (VGB) surgery remains unsatisfactory to this day. Despite years of improvements in surgical techniques and therapies administered, a re-occlusion of the graft is experienced in 10-12% of the cases within just few months.
We suggest that an efficient post-surgical therapy must be looked for at the genetic level. Accordingly, we propose a multiscale model that describes the graft healing with a particular focus on the genetic impact on the process of vascular adaptation in order to test in advance targeted gene therapies.
A key feature of our model is its capability of linking the genetic, cellular and tissue levels with feedback loops in such a way that every variation from an equilibrium point is reflected on all the other elements, creating in this way a highly organized loop.
Our multiscale model is based on two coupled components. First, a Dynamical System (DS) describes the adaptation of the vein bypass graft to mechanical stresses imposed by switching from a venous flow to an arterial one. Second, an Ordinary Differential Equations (ODEs) system replicates the complex regulatory cascade from upstream gene regulators to cellular events impacting the graft's adaptation. With the latter, several levels of connectivity are explored, i.e. regulators-mediators, mediators-mediators, and finally mediators-cellular events.
The model was calibrated at various levels on experimental data from rabbit model. This is a complex process, where a heterogeneous set of data at gene, cellular and anatomy level can be used either for calibration or for further validations. The validation on experimental data showed a high degree of accuracy, with a percentile error less than 1%.
Having a hand on the upstream regulators level will allow us to test several gene therapies by targeting single genes instead of group of genes as done in a previous work by our group, guarantying in this way a more realistic therapy simulation.
Our in silico model is accurate, fast to run, easy to use and predictive. Its ability to test in advance the outcome of a broad range of gene therapies can dramatically fasten the research aimed to prolong the life expectancy of vein graft bypasses.

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